UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/738,049	12/15/2000	David R. Kaplan	071957-0903	2323

30542 7590 07/01/2003

FOLEY & LARDNER
P.O. BOX 80278
SAN DIEGO, CA 92138-0278

EXAMINER
CHEU, CHANGHWA J

ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 07/01/2003

17

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/738,049	KAPLAN, DAVID R.	
	Examiner	Art Unit	
	Jacob Cheu	1641	

-- The MAILING DATE f this communication appears on the cover sheet with the corresp ndence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-33* is/are pending in the application.

4a) Of the above claim(s) *34-61* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Amendment Entry

1. Applicant's amendment and response filed on 4/28/2003 in Paper No. 16 is acknowledged and has been entered. Applicant's arguments are considered but are moot in view of the new ground(s) of rejection.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 1-33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

With respect to claim 1, step (d), line 5, "and that is isotype/subtype" is vague and confusing. It is unclear what "that" refers to, either the analyte or the immunoglobulin.

Similarly, claim 2, step (c), line 5, "that is isotype/subtype" shares the same problem as in claim 1.

With respect to claim 3, line 2, "then a signal" should change to "than a signal."

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

5. Claims 1, 2-5, 10, 14-18, 25-26, 28-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Karkmann et al. (J. Immu. Methods. 1999) in view of Todisco et al.. (Blood (2000) 95: 535-42)

Karkmann et al. teach a method of detecting intracellular analyte by applying tyramine-based amplification signal in flow cytometry. Karkmann et al teach fixing and pemeabilizing blood cells with 0.5 saponin, and resuspend the cells in a buffer containing bovine serum albumin. (page 114, Right column to page 115, Left column) Karkmann et al teach staining the cells with fluorescein-labeled antibodies against the analyte which is linked to horseradish-peroxidase directly or indirectly by biotinylation, i.e. avidin-biotin, and thereafter adding tyramine substrate. (page 115, Right column) However, Karkmann et al. do not specifically disclose using an immunoglobulin (isotype or subtype matched) that does not specifically bind to the intracellular analyte as a standard negative control and have at least 10-fold greater signal than the standard negative control.

Nevertheless, the notion of using the standard negative control is well-known in the art of flow cytometry. (See Todisco, Abstract) Todisco et al. teach applying isotype-matched "nonreactive antibody" (immunoglobulin) as a negative control, i.e. to reduce nonspecific

bindingin, in flow cytometry to detect antigens from patients' bone marrow cells. (page 535, Method and Materials; page 537, Left column) Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have recognized the advantage of the standard negative control such as nonreactive isotype/sutype antibodies as taught by Todisco et al. and provided the method of Karkmann et al. with the standard negative control in detecting the analyte of interest with a reasonable expectation of 10-fold greater signal compared to the standard since the 10-15 fold signal from Karkmann et al. reference would be even greater when incorporating with the standard negative control method as taught by Todisco et al.

With respect to claims 3-4, the 20, or 50-fold greater signal compared to that of the standard flow cytometry, since applicant has not disclosed that the specific limitations recited in the instant claims 3-4 are for any particular purpose or solve any stated problem, absent unexpected results, it would have been obvious to one of ordinary skill to have provided the method of Karkmann et al. with the standard negative control to improve detection signals as taught by Todisco et al with a reasonable expectation of success because the prior art teaches that tyramide amplification methods often vary according to the type of the cell sample being analyzed and various matrices and parameters appear to work equally well.

6. Claims 1-2, 5, 11-19, and 23-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lollini et al. (Immunological Blackboard, 1998) in view of Todisco et al..

Lollini et al. teach a method and kit for detecting intracellular analyte, i.e. p53, in osteosarcoma cells wherein flow cytometric detection is performed after tyramide signal amplification (Abstract). Lollini et al. also teach culturing cells in fetal bovine albumin, fixing cells with methanol, and permeabilizing cells with methanol or acetone. Lollini et al. also teach similar tyramide amplification by using an antibody against the analyte, then adding peroxidase-conjugated F(ab')2 anti-mouse IgG, and subsequently placing fuorescein tyramide sustrate to catalyze the deposition of tyramide on cells for detection.

Lollini et al. do not specifically teach using isotype/subtype immuglobulin as a standard negative control in the assay. Nonetheless, Lollini et al. recognize a potential problem for this report: "[t]he main problem appeared to be a high level of spontaneous activation and *non-specific binding* of the fluorescent substrate to live cell membranes."

Todisco et al. teach using isotype-matched "nonreactive antibody" as a negative control in flow cytometry to detect antigens from patients' bone marrow cells. (page 535, Method and Materials; page 537, Left column) Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have provided the method of Lollini et al. with the nonreactive isotype/sutype antibodies as taught by Todisco et al. as the negative control to improve the accuracy of the method in detecting the analyte of interest because using isotype/subtype antibodies as negative control is a common knowledge in the art to reduce nonspecific binding, and one skilled in the art would be motivated to do so if encounter in a similar problem as that of Lollini et al.

7. Claims 6-9, and 20-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Karkmann et al. or Lollini et al.

Both Karkmann and Lollini et al. references have been discussed but both references do not specifically teach using medium comprising 50% fetal bovine serum or 95% fetal bovine serum and 0.2% saponin as recited in claims 6-9 and 20-22. However, it has been long held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller,* 105 USPQ 233. It has also been held that discovering an optimum value of a result effective variable involves only routine skill in the art. *In re Boesch*, 617 F.2d 272, 205 USPQ 215 (CCPA 1980) Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to manipulate the assay by varying ranges of medium in order to optimize the result.

Response to Arguments

8. Applicant's argument filed on May 1, 2003 has been considered but are moot in view of the new ground of rejections of this Office Action. With respect to the applicant's Declaration filed on October 21, 2002, examiner directs applicant's attention to the reasons set forth in this Office Action.

Conclusion

9. No claim is allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jacob Cheu whose telephone number is 703-306-4086. The examiner can normally be reached on 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on 703-305-3399. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4556 for regular communications and 703-308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-305-3399.

Jacob Cheu
Examiner
Art Unit 1641

***

June 18, 2003

LONG V. LE
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

06/27/03